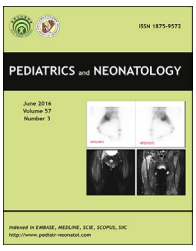
Pediatrics and Neonatology (2016) 57, 201–206

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



ORIGINAL ARTICLE

Epidemiology of Hirschsprung's Disease in Taiwanese Children: A 13-year Nationwide Population-based Study

Shu-Ti Chia [a,b], Solomon Chih-Cheng Chen [a,c,d], Chin-Li Lu [c,e], Shew-Meei Sheu [c], Hsing-Ching Kuo [a,*]

[a] *Department of Pediatrics, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi City, Taiwan*
[b] *The Institute of Clinical Medicine of National Cheng Kung University, Tainan City, Taiwan*
[c] *Department of Medical Research, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi City, Taiwan*
[d] *Department of Pediatrics, School of Medicine, Taipei Medical University, Taipei City, Taiwan*
[e] *Department of Public Health, College of Medicine, National Cheng Kung University, Tainan City, Taiwan*

Received Dec 24, 2014; received in revised form Mar 13, 2015; accepted Apr 27, 2015
Available online 22 October 2015

Key Words
Down syndrome;
enterocolitis;
incidence;
megacolon;
sex ratio

Background: Hirschsprung's disease (HD) is an important colon disease in children. The aim of this study is to describe the epidemiological features of HD in Taiwanese children.
Methods: We conducted a study from the Taiwan National Health Insurance Research Database and analyzed cases who received surgical intervention between 1998 and 2010 due to HD (International Classification of Diseases, 9th Revision, Clinical Modification 751.3) or megacolon (International Classification of Diseases, 9th Revision, Clinical Modification 564.7). The incidence, sex ratio, age at the surgical intervention, associated complication, and medical expenditures were analyzed.
Results: There were a total of 629 HD cases, including 458 boys and 171 girls, with an overall incidence of 2.2 per 10,000 live births. The male-to-female incidence ratio was 2.38. There was no secular trend of incidence across the years. Seventy-two percent of cases received surgical treatment before the age of 1 year. The younger cases had higher operation-related medical expenditures. Those patients with preoperative enterocolitis (EC) had a higher possibility of postoperative EC than those patients without preoperative EC (34.6% vs. 24.3%, $p = 0.013$). There were 169 (26.9%) HD cases with additional anomalies, the most common being gastrointestinal and circulatory system anomalies. Of these, 12 (1.9%) cases were Down syndrome.

* Corresponding author. Ditmanson Medical Foundation Chia-Yi Christian Hospital, Number 539, Zhongxiao Road, East District, Chia-Yi City 60002, Taiwan.
E-mail address: pietaa@yahoo.com.tw (H.-C. Kuo).

http://dx.doi.org/10.1016/j.pedneo.2015.04.016

Conclusion: The incidence of HD in Taiwanese children, a majority Chinese population, was one per 4545 live births with a male predominance. Preoperative EC was a significant factor that was associated with postoperative EC. The percentage associated with Down syndrome was relatively low, probably due to a prenatal screening program.

1. Introduction

Hirschsprung's disease (HD) is a malformation of the hindgut, characterized by congenital aganglionosis with variable proximal extension manifested by a megacolon.[1] HD is usually diagnosed shortly after birth because of the absence of meconium passage within 48 hours of delivery, or other symptoms including bile-stained vomitus, explosive stools after anal stimulation, distention of the abdomen, dilated bowel loops upon abdominal X-ray examination, or diarrhea.[1] Although most HD cases are diagnosed in the newborn period or during infancy, some milder cases are well tolerated and diagnosed after infancy. Therefore, for those children with chronic constipation since birth, a diagnosis of HD should be considered.[2]

The incidence of HD varies across different geographic or ethnic populations. One early cohort survey in British Columbia, from 1964 to 1982, using the records of a health surveillance registry, estimated the incidence for HD as one in 4417 live births.[3] Another survey in the US, between 1969 and 1977, found the incidence of HD to be one in 5376 births.[4] In Japan, the incidence of HD, between 1978 and 1982, was one in 4697 births.[5] However, the incidence of HD in Taiwan, with its majority ethnic Chinese population, has not yet been investigated.

The objectives of this study were to explore the epidemiological features, including the incidence of live births, the sex ratio, the occurrence of complications, and associated anomalies of HD cases in Taiwanese children over a period of 13 years (1998—2010).

2. Methods

2.1. Ethical approval

Taiwan National Health Insurance Research Database is a nationwide population-based reimbursement database. Due to the regulations of the Personal Electronic Data Protection Law of Taiwan, the identification (ID) numbers of all of the persons and hospitals in this database were encrypted so as to be unrecognizable from the original ID numbers. New ID numbers permitted us to analyze a patient's data while maintaining their anonymity. Thus, this study represents an analysis of deidentification secondary data. The Institutional Review Board of Ditmanson Medical Foundation Chia-Yi Christian Hospital waived the requirement for written informed consent from the patients involved and approved this study.

2.2. Cases identification

Taiwan, an island country with approximately 23 million people, has a National Health Insurance (NHI) system that covers $>$ 99.5% of the population.[6] Because of its high coverage rate, the NHI health care database contains representative information to describe the epidemiological features of some particular diseases[7,8] and has already produced many publications.[9] From this database, we identified HD or megacolon cases as having the diagnosis listed as any one of the first three major diagnoses according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM; ICD9 Data.com, 2012). The selected cases with ICD-9-CM 751.3 (HD) or 564.7 (megacolon) were further confirmed as HD cases when they underwent a definite surgical procedure. The ICD-9-CM-OP codes of these surgical procedures are 484 (pull-through resection of the rectum), 484.1 (endorectal pull-through resection of the rectum), 484.9 (abdominoperineal pull-through resection of the rectum), 486.5 (Duhamel resection of the rectum), and 486.9 (rectal resection). Some HD patients were sensitive for severe enterocolitis (EC); however, there was no clear definition to identify Hirschsprung's-associated EC. Therefore, we identified those hospitalized patients with discharge codes of 558.2, 558.9, 009.0, 009.1, 009.2, and 009.3 as EC-related codes. Any HD case who had been diagnosed as having a congenital anomaly on admission on their medical records, were identified with ICD-9-CM codes between 740.x and 758.x.

2.3. Incidences according to age, sex, and calendar year

Children with a hospitalized diagnosis of HD or megacolon born between January 1998 and December 2010 and having one of above-mentioned surgical procedures were identified from the NHI Research Database. We sorted the new ID numbers and carefully checked the patients' birth dates, admission dates, and discharge dates. The incidence of HD or megacolon was calculated as the number of cases divided by the total number of live births of the corresponding sex-group in each calendar year. The medical costs for operations and related hospital stays were compared among five age groups: (1) $\leq$ 1 month; (2) $>$1—3 months; (3) 4—6 months; (4) 7—12 months; and (5) 1—15 years of age. The currency exchange rate of USD and TWD used in this study was 1:30.

2.4. Statistical analysis

Incidence was expressed as the number of HD or megacolon cases per 10,000 live births. Age- and sex-specific population sizes were obtained from the Population Statistics of the Ministry of Interior in Taiwan.[10] Poisson regression analysis was conducted to test the secular trend for the incidence of HD. Cochrane–Armitage trend test was performed to test the increasing trend of the incidence of preoperative EC by age. Fisher's exact test was used to compare the occurrence of postoperative EC among those who had preoperative EC across age groups. The data were analyzed using Microsoft Excel and IBM SPSS Statistics, version 21.0 (International Business Machines Corp. Armonk, New York 10504, USA).

3. Results

3.1. Case numbers and incidence

A total of 629 HD cases, including 458 boys and 171 girls, were identified from 1998 to 2010. The incidence of HD cases was 2.2 per 10,000 live births (equal to 1:4545), with an overall male-to-female incidence ratio of 2.38 (Table 1). Secular trend by Poisson regression model did not show any significance in either sex.

3.2. Distribution of HD cases by age

Among all cases, less than one-fifth of patients were operated within the 1st month of life, and 72% of the cases were operated before the age of 1 year (Figure 1). The medical expenditures were gradually decreased as age increased (Table 2).

Table 1 Number and incidence of Hirschsprung's disease in Taiwan from 1998–2010.

Birth	Number			Incidence (per 10,000)			
Y	Total	Male	Female	Total	Male	Female	M/F ratio
1998	63	40	23	2.5	3.0	1.9	1.58
1999	57	41	16	2.1	2.9	1.2	2.42
2000	56	45	11	1.9	2.9	0.8	3.63
2001	59	38	21	2.4	3.0	1.8	1.67
2002	54	41	13	2.3	3.3	1.2	2.75
2003	48	33	15	2.2	2.9	1.5	1.93
2004	54	42	12	2.6	3.9	1.2	3.25
2005	43	33	10	2.2	3.2	1.1	2.91
2006	47	36	11	2.4	3.6	1.2	3.00
2007	36	28	8	1.9	2.8	0.9	3.11
2008	47	30	17	2.5	3.1	1.9	1.63
2009	37	27	10	2.0	2.8	1.1	2.55
2010	28	24	4	1.8	2.9	0.5	5.80
Total	629	458	171	2.2	3.1	1.3	2.38

M/F ratio = male-to-female incidence ratio.

3.3. Rate of pre- and postoperative EC

There were 153 (24.3%) of HD cases with a diagnosis of preoperative EC, and 169 (26.9%) cases with postoperative EC (Table 3). The percentage of postoperative EC among patients with preoperative EC was 34.6% (53/153), which was significantly higher than the 24.3% in those patients without preoperative EC (116/476, $p = 0.013$). Although the HD cases ($\leq$ 1 month) with preoperative EC did not have any postoperative EC, the occurrence of postoperative EC among cases with preoperative EC was not different across the ages of operation ($p = 0.437$ in Table 3).

3.4. Rate of associated congenital anomalies

Among all cases, there were 169 (26.9%) HD cases with some additional anomalies containing the ICD-9-CM code from 740.x to 758.x. Gastrointestinal anomalies, excluding HD itself, and circulatory system anomalies were the most frequent additional anomalies as shown in Table 4. Among 18 cases with a chromosome anomaly, 12 (66.67%) were Down syndrome. The detailed diagnoses and ICD-9-CM codes are shown in Table 4.

4. Discussion

The present study provided nationally-representative epidemiological features of HD based on a NHI claims dataset. The incidence of HD cases was 2.2 per 10,000 live births in Taiwan. The incidence in boys was higher than that in girls, and the time trend for both sexes was constant. Almost three-fourths of patients received operations during the 1st year of life. The occurrences of postoperative EC among cases with preoperative EC were similar across different age groups. In the HD-associated anomalies, the digestive and circulatory systems were the most common.

The incidence of HD in this study was one in 4545, which is similar to the incidence of HD in British Columbia (1/4417)[3] and Japan (1/4697)[5], but higher than that in US (5376)[4] and Denmark (1/7165).[11] The present study did not find any time-trend in the incidence of HD over the study period of 13 years (Table 1), which agreed with previous findings.[4] HD, like other childhood diseases, such as intussusception and pyloric stenosis, occurs predominantly in boys.[7,8,12–14] Twenty-eight percent of the HD patients were operated after the age of 1 year, which was higher than in previous studies.[15,16] This could be due to milder symptoms of these patients. However, this reminds us that HD should be considered in patients who present with symptoms of chronic constipation from birth.[2]

In our study, the 26.9% of HD cases with additional anomalies (Table 4) were within the range (11–30%) reported by previous studies.[3,17–19] Consistent with the study of Spouge and Baird,[3] cardiovascular and gastrointestinal anomalies were the major anomalies in this study. The most common chromosomal abnormality associated with HD is Down syndrome.[20] Down syndrome has a higher frequency among HD-affected individuals but not among their unaffected siblings, and this increase does not seem to be associated with maternal age.[11,21] The occurrence of Down syndrome in HD cases varied widely with the incidence

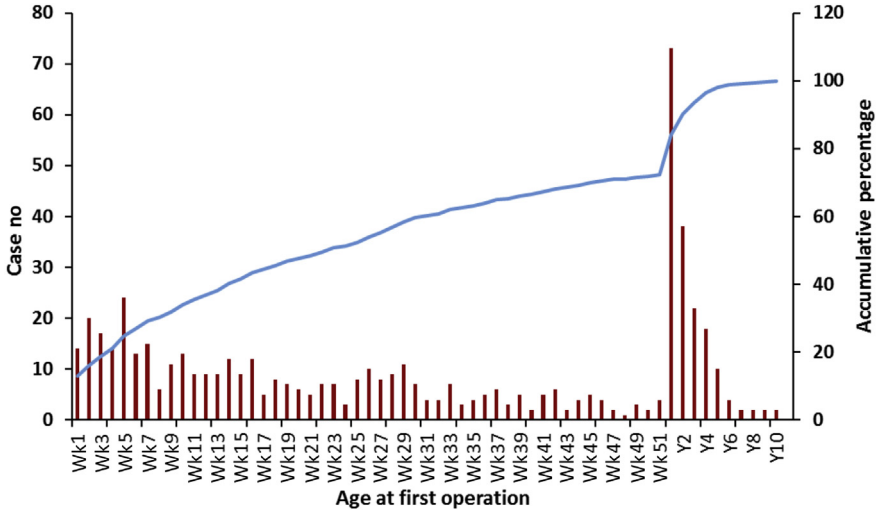


Figure 1 Number and accumulated percentage of the operated cases with Hirschsprung's disease by age. Wk = week, Y = year.

Table 2 Case number and medical expenditures of Hirschsprung's disease cases stratified by age.

Age of operation (mo)	Male *N* (%)	Female *N* (%)	Total *N* (%)	Med. Expenditure (US$)
≤1	95 (20.7)	27 (15.8)	122 (19.4)	6479 (4576–10,162)
>1–3	76 (16.6)	32 (18.7)	108 (17.2)	4968 (3973–7021)
4–6	77 (16.8)	22 (12.9)	99 (15.7)	4525 (3422–6021)
7–12	93 (20.3)	31 (18.1)	124 (19.7)	3977 (3220–5481)
>12	117 (25.6)	59 (34.5)	176 (38.0)	3691 (3160–5481)
Total	458 (100.0)	171 (100.0)	629 (100.0)	4,513 (3397–6897)

Med. = medical.

ranging from 0.64% to 16.25%.[22] In this present study, only 12 (1.91%) of HD cases were accompanied with the diagnosis of Down syndrome (Table 4). The reason for the much lower rate of Down syndrome in Taiwanese children with HD may be due to the Down syndrome screening program implemented from 2001. Lin et al[23] (2013) demonstrated that the incidence of Taiwanese Down syndrome has dramatically decreased from 22.3 in 2001 to 7.8 in 2010 per 100,000 live births.

Hirschsprung's-associated EC can occur before diagnosis of HD and after definitive operative procedure.[24] EC can be the most serious complication to occur in about one-third of HD cases and potentially result in high morbidity and mortality.[25,26] The presence of EC can significantly increase the frequency of hospital admissions, the duration of hospital stays, and medical costs.[27] The occurrence of preoperative EC among all HD cases in this study averaged 24.3% (Table 3). Notably, the occurrence of postoperative EC

Table 3 Relationship between age at operation and the percentage of postoperative enterocolitis among patients with preoperative enterocolitis.

Age of operation (mo)	Total (*n*)	Preop EC (*n*)	Postop EC (+) among preop EC (+), *n* (%)[1]	Postop EC (−) among preop EC (+), *n* (%)[a]	*p*[b]
≤1	122	6	0 (0.0)	6 (100.0)	0.437
>1–3	108	19	8 (42.1)	11 (57.9)	
4–6	99	19	6 (31.6)	13 (68.4)	
7–12	124	44	16 (36.4)	28 (63.6)	
>12	176	65	23 (35.4)	42 (64.6)	
Total	629	153	53 (34.6)	100 (65.4)	

EC = enterocolitis.
[a] Percentage to the case number of preoperative enterocolitis.
[b] Fisher's exact test was used to compare the percentages of postoperative enterocolitis among cases with preoperative enterocolitis across age groups.

Table 4 Case number and percentage of Hirschsprung's disease cases with associated congenital anomalies among 629 Hirschsprung's disease cases.

Congenital anomalies	ICD-9-CM code	*N*	%
Nervous system	740.x–742.x	10	1.59
Eye, ears, face, & neck	743.x–744.x	6	0.95
Circulatory system	745.x–747.9	55	8.74
Respiratory system	748.x	14	2.23
Digestive system[a]	749.x–751.x	97	15.42
Genital organs	752.x	18	2.86
Urinary system	753.x	16	2.54
Musculoskeletal system	754.x–756.x	16	2.54
Chromosome anomaly[b]	758.x	18	2.86
Total		169	26.87

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.
[a] Digestive system did not include Hirschsprung's disease itself (ICD-9 = 751.3).
[b] Among 18 cases with chromosome anomaly, 12 cases were Down syndrome.

among the cases with preoperative EC was significantly higher than that in cases without preoperative EC, indicating preoperative EC to be an important factor associated with the occurrence of postoperative EC. Although the medical expenditures of operated cases decreased with age (Table 2), the occurrence of postoperative EC among those patients with preoperative EC remained similar at different ages of operation (Table 3). Thus, the possibility of postoperative EC would not be a concern for the selection of operation time.

4.1. Limitations

Longer aganglionic segments may correlate with a higher possibility of additional anomalies.[17] Unfortunately, we did not have the pathological information about the length of the aganglionic segment in our HD cases because the NHI reimbursement database was not originally designed for academic research. In addition, delayed complications or mortality occurring after a long period of time may be missed in data,[28] even though the observational period has been up to 13 years in this study. Despite the limitations above, we believe that the NHI database is still very representative and can provide useful epidemiological information about HD on a national scale.

4.2. Conclusion

This study used a nationwide database to describe the epidemiological features of HD. The incidence of HD in Taiwan, with its majority ethnic Chinese population, is one in 4545. The overall male-to-female incidence ratio is 2.38:1. Preoperative EC was a significant factor associated with postoperative EC. There were higher medical expenditures for HD cases at younger ages, whereas the percentage of postoperative EC among the patients with preoperative EC remained similar at different ages. The lower rate of Down syndrome in Taiwanese children with HD may be due to the Down syndrome screening policy.

Conflicts of interest

None declared.

References

1. Kenny SE, Tam PK, Garcia-Barcelo M. Hirschsprung's disease. *Semin Pediatr Surg* 2010;**19**:194–200.
2. Doodnath R, Puri P. A systematic review and meta-analysis of Hirschsprung's disease presenting after childhood. *Pediatr Surg Int* 2010;**26**:1107–10.
3. Spouge D, Baird PA. Hirschsprung disease in a large birth cohort. *Teratology* 1985;**32**:171–7.
4. Goldberg EL. An epidemiological study of Hirschsprung's disease. *Int J Epidemiol* 1984;**13**:479–85.
5. Ikeda K, Goto S. Diagnosis and treatment of Hirschsprung's disease in Japan. An analysis of 1628 patients. *Ann Surg* 1984;**199**:400–5.
6. *The National Health Insurance Statistics, Taiwan*. Taiwan: Bureau of National Health Insurance, Department of Health, Executive Yuan; 2011.
7. Leong MM, Chen SC, Hsieh CS, Chin YY, Tok TS, Wu SF, et al. Epidemiological features of infantile hypertrophic pyloric stenosis in Taiwanese children: a nation-wide analysis of cases during 1997–2007. *PLoS One* 2011;**6**:e19404.
8. Chen SC, Wang JD, Hsu HY, Leong MM, Tok TS, Chin YY. Epidemiology of childhood intussusception and determinants of recurrence and operation: analysis of national health insurance data between 1998 and 2007 in Taiwan. *Pediatr Neonatol* 2010;**51**:285–91.
9. *National Health Insurance Research Database*. Taiwan: National Health Research Institutes; 2013.
10. *Statistical Yearbook of Interior. Taipei*. Taiwan: Department of Statistics, Ministry of the Interior, Executive Yuan; 2014. Available at http://sowf.moi.gov.tw/stat/year/elist.htm. Accessed December 20, 2014.
11. Russell MB, Russell CA, Niebuhr E. An epidemiological study of Hirschsprung's disease and additional anomalies. *Acta Paediatr* 1994;**83**:68–71.
12. Jung PM. Hirschsprung's disease: one surgeon's experience in one institution. *J Pediatr Surg* 1995;**30**:646–51.
13. Moore SW, Zaahl MG. A review of genetic mutation in familial Hirschsprung's disease in South Africa: towards genetic counseling. *J Pediatr Surg* 2008;**43**:325–9.
14. Marty TL, Seo T, Matlak ME, Sullivan JJ, Black RE, Johnson DG. Gastrointestinal function after surgical correction of Hirschsprung's disease: long-term follow-up in 135 patients. *J Pediatr Surg* 1995;**30**:655–8.
15. Ziad F, Katchy KC, Al Ramadan S, Alexander S, Kumar S. Clinicopathological features in 102 cases of Hirschsprung disease. *Ann Saudi Med* 2006;**26**:200–4.
16. Arshad A, Powell C, Tighe MP. Hirschsprung's disease. *BMJ* 2012;**345**:e5521.
17. Ikeda K, Goto S. Additional anomalies in Hirschsprung's disease: an analysis based on the nationwide survey in Japan. *Z Kinderchir* 1986;**41**:279–81.
18. Ryan ET, Ecker JL, Christakis NA, Folkman J. Hirschsprung's disease: associated abnormalities and demography. *J Pediatr Surg* 1992;**27**:76–81.
19. Ieiri S, Higashi M, Teshiba R, Saeki I, Esumi G, Akiyoshi J, et al. Clinical features of Hirschsprung's disease associated with Down syndrome: a 30-year retrospective nationwide survey in Japan. *J Pediatr Surg* 2009;**44**:2347–51.

20. Menezes M, Puri P. Long-term clinical outcome in patients with Hirschsprung's disease and associated Down's syndrome. *J Pediatr Surg* 2005;**40**:810—2.
21. Badner JA, Sieber WK, Garver KL, Chakravarti A. A genetic study of Hirschsprung disease. *Am J Hum Genet* 1990;**46**: 568—80.
22. Friedmacher F, Puri P. Hirschsprung's disease associated with Down syndrome: a meta-analysis of incidence, functional outcomes and mortality. *Pediatr Surg Int* 2013;**29**: 937—46.
23. Lin SY, Hsieh CJ, Chen YL, Shaw SW, Lin MW, Chen PC, et al. The impact of Down syndrome screening on Taiwanese Down syndrome births: a nationwide retrospective study and a screening result from a single medical centre. *PLoS One* 2013; **8**:e75428.
24. Pastor AC, Osman F, Teitelbaum DH, Caty MG, Langer JC. Development of a standardized definition for Hirschsprung's-associated enterocolitis: a Delphi analysis. *J Pediatr Surg* 2009; **44**:251—6.
25. Singh SJ, Croaker GD, Manglick P, Wong CL, Athanasakos H, Elliott E, et al. Hirschsprung's disease: the Australian Paediatric Surveillance Unit's experience. *Pediatr Surg Int* 2003;**19**:247—50.
26. Elhalaby EA, Coran AG, Blane CE, Hirschl RB, Teitelbaum DH. Enterocolitis associated with Hirschsprung's disease: a clinical-radiological characterization based on 168 patients. *J Pediatr Surg* 1995;**30**:76—83.
27. Hackam DJ, Filler RM, Pearl RH. Enterocolitis after the surgical treatment of Hirschsprung's disease: risk factors and financial impact. *J Pediatr Surg* 1998;**33**:830—3.
28. Tander B, Rizalar R, Cihan AO, Ayyildiz SH, Ariturk E, Bernay F. Is there a hidden mortality after one-stage transanal endorectal pull-through for patients with Hirschsprung's disease? *Pediatr Surg Int* 2007;**23**:81—6.